

Complement Component 3 (C3)

Deficiency — Comprehensive Disease Characteristics Report

Disease: Complement Component 3 Deficiency **MONDO ID:** MONDO:0013417 · **OMIM:** #613779 (disease), 120700 (gene) · *Orphanet:* ORPHA:280133 · *DOID:* 8354 · *NCIT:* C9468 · *GARD:* 0016489 · *UMLS:* C3151071 · *MeSH:* C565169 · *MedGen:* 462421 *Category:** Mendelian (autosomal recessive inborn error of immunity)

Summary

Complement component 3 (C3) deficiency is an **extremely rare autosomal-recessive inborn error of immunity** caused by biallelic loss-of-function variants in the C3 gene (HGNC:1318; chromosome 19p13.3; UniProt P01024). Fewer than 50 cases have been reported worldwide, making it one of the rarest of all complement deficiencies — which themselves comprise only ~1–10% of primary immunodeficiencies. The biochemical hallmark is **undetectable serum C3 with markedly reduced CH50 and normal C4**, reflecting failure of all three complement activation pathways at their convergence node ([PMID: 42445183](#)).

Because C3 is the central protein through which the classical, alternative, and lectin pathways all pass, its complete loss abolishes **C3b-thioester-mediated opsonization, C3a/C5a-driven inflammation, terminal membrane attack complex (MAC) formation, and immune-complex clearance and B-cell co-stimulation**. This produces a characteristic **dual clinical phenotype**: (1) recurrent, severe, invasive pyogenic infections by encapsulated bacteria (*Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*) with a predominance of respiratory/ENT disease, sepsis and meningitis; and (2) immune-complex-mediated disease, including SLE-like autoimmunity and membranoproliferative/mesangioproliferative glomerulonephritis. The autoimmune arm reflects the broader "complement–SLE hierarchy," in which early-complement-component deficiencies are the strongest known monogenic risk factors for lupus and are linked to type I interferon dysregulation.

There is **no curative therapy**. Management is preventive and supportive, centered on conjugate-polysaccharide vaccination against encapsulated bacteria and consideration of long-term antibiotic prophylaxis; analogous early-complement deficiencies show that early diagnosis plus prophylaxis can allow a near-normal life. A crucial clinical caveat is that **low serum C3 is far more often secondary** (deficiency of regulators factor H or factor I, C3 nephritic factor / C3 glomerulopathy, or classical-pathway consumption in SLE) than due to primary genetic C3 deficiency, which is defined by *undetectable* C3 with normal C4.

Key Findings

1. Disease definition, identifiers, and nature of evidence (F001, F010)

Complete C3 deficiency is an **ultra-rare autosomal-recessive inborn error of immunity** caused by homozygous or compound-heterozygous loss-of-function variants in C3. The authoritative MONDO definition (MONDO:0013417) describes "a rare genetic disorder with an autosomal recessive pattern of inheritance... caused by the ineffective or decreased biosynthesis of the third complement component, C3," with clinical signs appearing "within the first decade of life... consistent with the signs of recurrent systemic infection or immune complex disease." The definition further notes that "deficiency of serum C3 and its major cleavage product, C3b, will decrease the effective humoral immune response to encapsulated bacteria" and that C3 deficiency "also impairs clearance of circulating immune complexes and therefore predisposes to rheumatic and renal disease."

Cross-reference identifiers were verified against EBI OLS4/MONDO: OMIM 613779, Orphanet 280133, MeSH C565169, UMLS C3151071, MedGen 462421, DOID:8354, NCIT C9468, GARD 0016489, NANDO 2200782.

Synonyms / alternative names: C3 deficiency; complement component 3 deficiency, autosomal recessive; C3 classic complement early component deficiency; classic complement early component deficiency caused by mutation in C3.

Nature of the evidence: Because the disease is ultra-rare (<50 cases), most knowledge derives from **aggregated disease-level resources** (OMIM, Orphanet, MONDO, HPOA) and **individual case reports/small series** rather than large EHR cohorts. Mechanistic inferences are supported by model-organism (C3-knockout mouse) and in-vitro/structural studies, and by extrapolation from the better-characterized early-complement deficiencies (C1q, C2, factor H, factor I) ([PMID: 42445183](#)).

2. Clinical phenotype — infections plus immune-complex/autoimmune disease (F002, F011)

The clinical phenotype has two arms. In the infectious arm, patients suffer **recurrent severe pyogenic infections** with a predominance of the respiratory and otorhinolaryngological tracts, plus invasive disease (sepsis, meningitis) from encapsulated organisms. The index report notes that "both patients presented with chronic and recurrent infections, predominantly affecting the respiratory and otorhinolaryngological systems" ([PMID: 42445183](#)).

In the autoimmune/immune-complex arm, a subset develop **SLE-like disease** and **membranoproliferative/mesangioproliferative glomerulonephritis**. In a Saudi pediatric PID-lupus cohort, complement deficiency was the most frequent underlying PID, and "three patients had C3 deficiency" ([PMID: 33563058](#)). More broadly, "the genetic deficiency of any early component of the classical pathway (C1q, C1r/s, C2, C4) is often associated with autoimmune diseases" ([PMID: 25037634](#)).

Curated HPO phenotype annotations (OMIM:613779 / HPOA; primary source

):

P 15781264

Phenotype	HPO term	Noted frequency
Decreased circulating complement C3 concentration	HP:0005421	2/2
Recurrent bacterial infections	HP:0002718	1/1
Recurrent pneumonia	HP:0006532	2/2
Recurrent tonsillitis	HP:0011110	1/1
Recurrent fever	HP:0001954	1/1
Systemic lupus erythematosus	HP:0002725	1/1
Membranoproliferative glomerulonephritis	HP:0000793	—
Nephrotic syndrome	HP:0000100	—
Renal insufficiency	HP:0000083	—
Childhood onset	HP:0011463	—
Infantile onset	HP:0003593	—
Autosomal recessive inheritance	HP:0000007	—

Quality of life: No disease-specific QoL instruments (EQ-5D, SF-36) data are available for this ultra-rare disorder. Impact is driven by recurrent hospitalizations for invasive infection and, where present, by chronic kidney disease from glomerulonephritis.

3. Molecular/genetic information (F001, F005, F012)

- **Causal gene:** C3 (complement C3), HGNC:1318, NCBI Gene 718, Ensembl ENSG00000125730, cytoband **19p13.3**, protein-coding. OMIM gene *120700; disease #613779.
- **Protein:** UniProt **P01024**. Sequence length = **1663 aa precursor** (signal peptide 1–22; mature "Complement C3" chain = residues 23–1663 = **1641 aa**), processed into a β -chain (23–667, 645 aa) and α -chain (672–1663, 992 aa), with embedded fragments **C3a** (672–748), **C3b** (749–1663), **C3d** (1002–1303), and **C3f** (1304–1320). The 1663 (precursor) vs 1641 (mature) residue count discrepancy was reconciled: crystallographic studies describe the mature 1,641-residue protein ([PMID: 16177781](#)), while UniProt reports the full precursor.
- **Variant spectrum:** Nonsense, frameshift, missense, and splice-site variants have been reported. Example: a novel homozygous splice-site variant,

NM_000064.3:c.4030-1_4030delinsCT, in Moroccan patients (PMID: 42445183). Variants are **germline** and typically **loss-of-function** (ACMG pathogenic/likely pathogenic).

- **Functional consequence:** Absent or non-functional C3, with loss of the thioester-mediated opsonic function.
- **Modifier genes / epigenetics / chromosomal abnormalities:** No established disease-specific modifier genes or epigenetic signatures for primary C3 deficiency; the disorder is a single-gene, protein-truncating/loss-of-function condition rather than a structural/chromosomal syndrome. Allele frequencies of pathogenic C3 LoF variants are correspondingly rare in gnomAD given the <50-case worldwide total.

4. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. Biallelic loss-of-function variant in C3 (19p13.3)
 - leads to absent or non-functional C3 protein (undetectable serum C3; normal C4).
2. Loss of C3 abolishes the convergence node of all three complement pathways
 - results in failure to generate C3 convertase products C3a and C3b.
- 3a. [INFECTION BRANCH] No C3b thioester deposition on microbial surfaces
 - leads to loss of opsonophagocytosis (no CRIg/CR1-mediated phagocyte uptake)
 - and failure to assemble downstream C5 convertase / MAC
 - results in defective killing of encapsulated bacteria
 - leads to recurrent invasive pyogenic infection (pneumonia, sepsis, meningitis).
- 3b. [AUTOIMMUNE BRANCH] No C3b/iC3b tagging of apoptotic debris and immune complexes
 - leads to impaired clearance of circulating immune complexes and apoptotic cells
 - results in autoantibody formation and tissue immune-complex deposition
 - leads to SLE-like disease and membranoproliferative glomerulonephritis.
- 3c. [HUMORAL BRANCH, inferred from mouse] Loss of C3d-CR2/CD21 B-cell co-stimulation
 - leads to impaired antibody responses (esp. to polysaccharide antigens) and defective immune-complex trafficking to follicular dendritic cells
 - compounds susceptibility to encapsulated bacteria.

Central node mechanism (F003, F005). C3 is the convergence point of the classical, alternative, and lectin pathways. "Key complement functions (C3b-mediated opsonisation, C3a/C5a-driven inflammation, and membrane attack complex formation) underlie target-specific patterns of infectious risk" (PMID: 42175904). C3 is cleaved by C3 convertases into C3a (anaphylatoxin) and C3b, which deposits on surfaces via its reactive thioester and is recognized by phagocyte receptors; the complement receptor CRIg "binds to certain C3 cleavage products (C3b, iC3b, C3c)" (PMID: 38032267).

Protein-structural basis (F005). Crystal structures of native C3 and fragment C3c reveal a 1,641-residue protein built from thirteen domains in the α_2 -macroglobulin family. "Activation of component C3 (1,641 residues) is central to the three complement pathways and results in inflammation and elimination of self and non-self targets," and "a double mechanism prevents hydrolysis of the thioester group, essential for covalent attachment of activated C3 to target surfaces" (PMID: 16177781). In deficiency, the opsonic thioester chemistry is entirely absent.

Autoimmune mechanism and the complement-SLE hierarchy (F009). Early-complement-component deficiencies are the strongest monogenic risk factors for SLE, graded by cascade position (C1q > C4 > C2), with C3 deficiency also predisposing to lupus-like disease. Mechanistically, deficiency impairs complement-mediated clearance of apoptotic cells and immune complexes, producing autoantibodies, immune-complex deposition, and complement consumption. Monogenic complement-deficient SLE is frequently early-onset and refractory and is "linked to interferon pathway dysregulation," with C1q-deficient pediatric SLE responding to the anti-type-I-interferon-receptor antibody anifrolumab (PMID: 42597478).

Molecular pathways / GO & CL suggestions. Biological processes: **complement activation (GO:0006956)**, complement activation alternative pathway (GO:0006957), classical pathway (GO:0006958), lectin pathway (GO:0001867), **opsonization (GO:0008228)**, complement-dependent cytotoxicity, positive regulation of B-cell activation. Cellular component: **extracellular space (GO:0005615)** (C3 is a secreted plasma protein, mainly hepatocyte-derived). Chemical entity: the reactive thioester underlies covalent opsonization (CHEBI thioester class). Cell types involved: **hepatocyte (CL:0000182)** (primary synthesis), **macrophage (CL:0000235)** / **neutrophil (CL:0000775)** (opsonophagocytosis via complement receptors), **follicular dendritic cell (CL:0000442)** and **B cell (CL:0000236)** (immune-complex trafficking / co-stimulation).

5. Anatomical structures affected

- **Primary "organ":** the **blood/plasma complement system** (C3 is a circulating plasma glycoprotein); the **liver** (UBERON:0002107) is the principal site of C3 synthesis (hepatocytes).
- **Secondary organ involvement:** **lung/airway and ENT** (UBERON:0002048 lung; UBERON:0001557 upper respiratory tract) — recurrent pneumonia/tonsillitis; **meninges / CNS** (meningitis); **kidney** (UBERON:0002113) — membranoproliferative/mesangioproliferative glomerulonephritis, nephrotic syndrome, renal insufficiency; **skin and joints** in SLE-like disease.

- **Body systems:** immune/hematologic, respiratory, renal/genitourinary, and (via autoimmunity) musculoskeletal and integumentary.
- **Tissue/cell level:** glomerular mesangial and capillary structures (immune-complex deposition); phagocytes; follicular dendritic cells; B cells. **Subcellular:** C3 is secreted; opsonization occurs at the plasma-membrane/extracellular interface (GO:0005615).
- **Lateralization:** not applicable — a systemic circulating-protein deficiency; organ involvement (e.g., glomerulonephritis) is bilateral/systemic.

6. Temporal development (F001, F010, F011)

- **Onset:** Clinical signs typically appear **within the first decade of life** (HPO: Childhood onset HP:0011463; Infantile onset HP:0003593), consistent with recurrent systemic infection or immune-complex disease.
- **Onset pattern:** Chronic/recurrent rather than a single acute event; infections are episodic and recurrent.
- **Progression/course:** Lifelong; infection susceptibility persists. Autoimmune/renal complications may accumulate over time; glomerulonephritis can progress to chronic kidney disease.
- **Critical period / window of opportunity:** Early diagnosis enables vaccination and prophylaxis before major invasive infection — the key modifiable determinant of outcome.

7. Inheritance and population (F001, F008)

- **Inheritance: Autosomal recessive** (HP:0000007). Biallelic (homozygous or compound-heterozygous) loss-of-function C3 variants.
- **Penetrance/expressivity:** Biochemical penetrance of undetectable C3 is complete in biallelic LoF; clinical expressivity is variable (infection-predominant vs autoimmune-predominant vs, rarely, milder courses), consistent with other complement deficiencies.
- **Epidemiology:** Complement deficiencies comprise "between 1 and 10% of all primary immunodeficiencies" (PMID: 25037634); in some pediatric PID series as low as ~1.1% (PMID: 16836843). Complete C3 deficiency specifically is among the rarest — "fewer than 50 cases have been reported to date, and the genetic and phenotypic spectrum remains incompletely defined" (PMID: 42445183). It is widely **underdiagnosed** because few centers offer comprehensive complement analysis.

- **Founder effects / consanguinity:** Consanguinity and geographic clustering contribute to cases (e.g., multiple cases from the same region of Morocco). No large exact prevalence/incidence figures exist given rarity.
- **Sex ratio / age distribution:** No reliable sex predilection established for primary C3 deficiency; onset in childhood.

8. Diagnostics (F001, F007)

- **Laboratory hallmark: undetectable serum C3 with markedly reduced CH50 and normal C4** — "complement analysis showed undetectable C3 levels and markedly reduced CH50, with normal C4, consistent with isolated complete C3 deficiency" (PMID: 42445183). Both CH50 (classical) and AH50 (alternative) are low/absent because C3 is shared by both.
- **Functional/screening assays:** CH50 and AH50 total hemolytic complement assays as screens; individual component quantitation (C3, C4, factor B, factor H, factor I) to localize the defect. LOINC-codable assays include serum C3, C4, and total complement (CH50).
- **Genetic testing:** Confirmatory **single-gene C3 sequencing** or NGS panel/exome; "NGS identified a novel homozygous splice-site variant in the C3 gene" (PMID: 42445183). Cascade testing of relatives is appropriate.
- **Differential diagnosis (F007) — critical:** Low serum C3 is **more often secondary** than primary:
- **Factor H or factor I deficiency** → secondary C3 consumption via the unchecked alternative pathway. "A primary deficiency of factor H or I or both, will secondarily produce subnormal levels of C3 and factor B" (PMID: 6545495); and in CFI deficiency, "no detectable factor I (<2%) together with a low level of factor B and a moderately low level of factor H, indicating consumption secondary to the factor I deficiency" (PMID: 16138437).
- **C3 nephritic factor (C3NeF)** autoantibodies (dense deposit disease / C3 glomerulopathy): "autoantibodies in MPGN are termed C3 Nephritic Factor (C3NeF)... directed against a neoepitope of the complement C3 convertase C3bBb... C3NeF stabilizes this convertase and this results in C3 amplification and complement activation" (PMID: 19640589).
- **Classical-pathway consumption** in SLE / post-infectious / MPGN (typically *both* C3 and C4 low).

The distinguishing feature of **primary complete C3 deficiency** is undetectable C3 with **normal C4** and no evidence of a regulator defect or nephritic factor.

9. Outcome / Prognosis (F004)

- **No curative therapy exists.** Prognosis is determined largely by timeliness of diagnosis and institution of prophylaxis.
- With early diagnosis plus vaccination and antibiotic prophylaxis, outcomes in analogous early-complement deficiencies can approach normal life: in hereditary C2 deficiency, "early diagnosis, use of vaccinations and antibiotic prophylaxis may allow a normal life" ([PMID: 32164349](#)).
- Major morbidity/mortality drivers: invasive infection (sepsis, meningitis) by encapsulated bacteria, and chronic kidney disease where immune-complex glomerulonephritis develops.
- No disease-specific 5-/10-year survival statistics exist given rarity; prognostic factors are infection burden, presence/severity of glomerulonephritis, and adherence to prophylaxis.

10. Treatment (F004)

There is **no causative/curative treatment** for hereditary complement component deficiencies. Standard of care is **preventive and supportive**:

- **Vaccination (primary prophylaxis):** conjugate vaccines against **meningococcus**, **pneumococcus** (conjugate polysaccharide), and **Haemophilus influenzae type b**. "Prophylaxis with conjugate polysaccharide vaccines is recommended and antibiotic prophylaxis should be considered in individual cases" ([PMID: 28078901](#)).
- **Antibiotic prophylaxis:** long-term or case-by-case.
- **Pathogen targets:** "the most frequent pathogens are Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae" ([PMID: 37356020](#)).
- **Autoimmune/renal manifestations:** managed with standard immunosuppression for SLE/ glomerulonephritis. By extrapolation from monogenic complement-deficient SLE, **type I interferon-targeted therapy (anifrolumab)** is an emerging option ([PMID: 42597478](#)).
- **NCIT intervention terms:** Pneumococcal Vaccine (NCIT C1764), Meningococcal Vaccine, Haemophilus b Conjugate Vaccine, Antibiotic Therapy (NCIT C15844), Immunosuppressive Therapy.

11. Prevention (F004)

- **Primary:** immunization against encapsulated bacteria (see above); risk awareness.
- **Secondary:** early diagnosis via complement screening in children with recurrent invasive infection or early/atypical SLE; cascade testing of relatives.

- **Tertiary:** antibiotic prophylaxis, prompt treatment of febrile illness, surveillance for renal disease.
- **Counseling:** autosomal-recessive genetic counseling; carrier testing in consanguineous families; prenatal/preimplantation options where a familial variant is known.

12. Model organisms (F006)

C3-knockout (C3^{-/-}) mice (*Mus musculus*; NCBI Gene C3 12266) recapitulate opsonization and humoral defects:

- **Polysaccharide antibody defect:** "Mice deficient in C3 or Cr2 had an impaired primary immune response to III-PS. The defective response was characterized by low IgM levels and the lack of an isotype switch from IgM to IgG Ab production" (PMID: 12496386) — directly relevant to vaccine responsiveness in deficient patients.
- **Immune-complex trafficking defect:** "Capture of antigen by MZ B cells as well as antigen deposition on FDC was severely impaired in mice lacking C1q or C3" (PMID: 28710441).
- **Tissue inflammation phenotype:** "C3-deficient mice developed more severe pulmonary inflammations than wild type controls" in an AT1R-induced systemic sclerosis model (PMID: 39737181), highlighting a context-dependent protective/regulatory role for C3 in tissue.

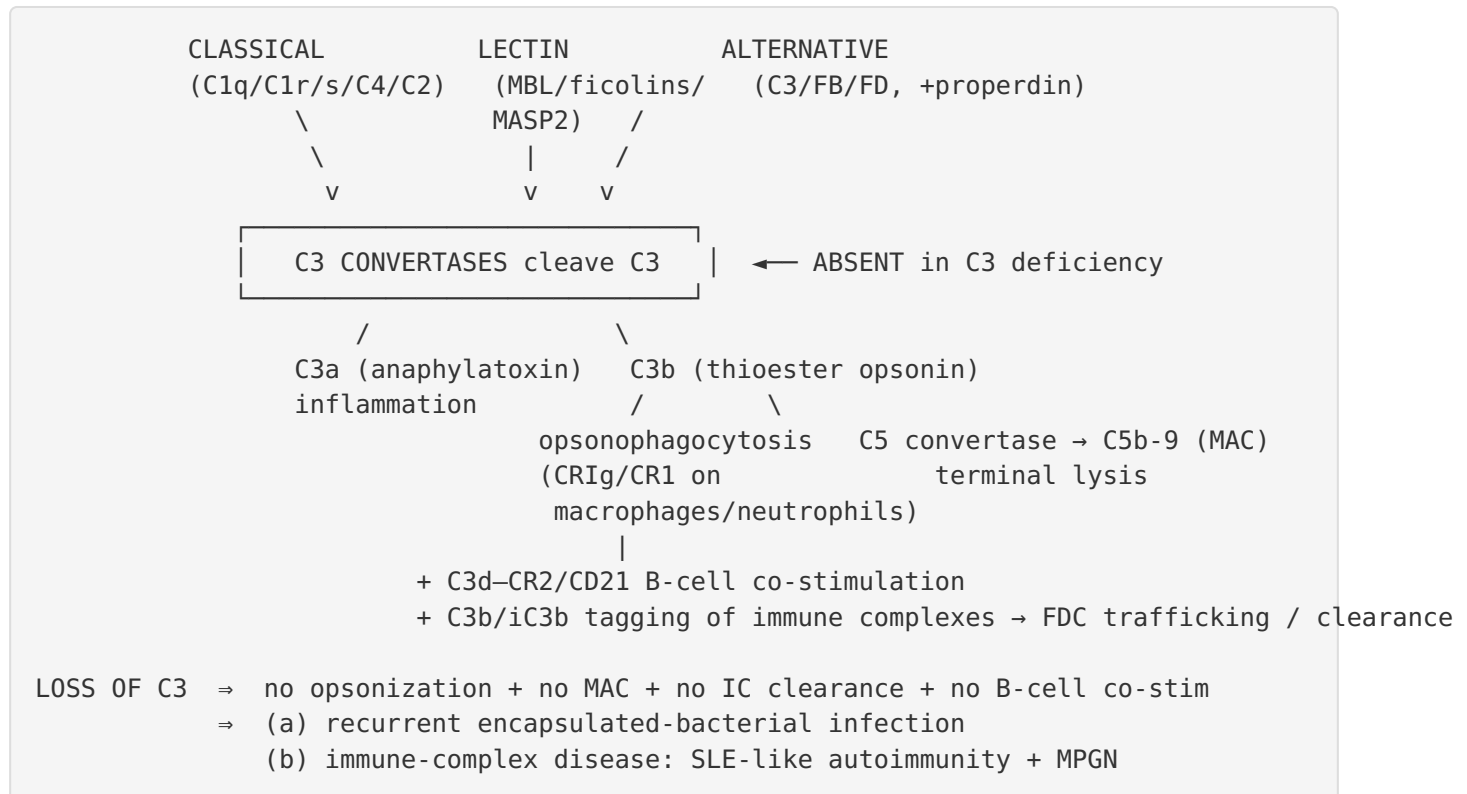
Limitations of models: Mouse C3 knockouts capture opsonization, humoral, and immune-complex-clearance defects but do not fully reproduce the human spectrum of recurrent encapsulated-bacterial invasive disease plus SLE-like autoimmunity; genetic background and specific infection/immunization challenges strongly influence phenotype.

13. Other species / comparative biology

- **Orthologous gene:** mouse C3 (NCBI Gene 12266); C3 is highly evolutionarily conserved across vertebrates as a core innate-immune molecule of the α_2 -macroglobulin/thioester-containing protein family (PMID: 16177781 — "insights into the function and evolution of immunity").
- **Natural disease:** Naturally occurring C3 deficiency has historically been described in domestic animals (e.g., dogs); no curated OMIA entry was validated in this investigation. Zoonotic transmission is **not applicable** (a genetic deficiency, not a transmissible disease).

Mechanistic Model / Interpretation

The entire disease flows from the position of C3 as the **single convergence node** of the complement system. The following schematic integrates the findings:



Two features make C3 deficiency mechanistically distinctive among complement defects. First, because C3 is downstream of all three initiating pathways but upstream of the entire terminal cascade, its loss is **more complete** than that of any single upstream initiator — both CH50 and AH50 collapse. Second, the **dual phenotype** is not coincidental: the same C3b/iC3b chemistry that opsonizes bacteria also tags apoptotic debris and immune complexes for clearance, so its loss simultaneously creates infection susceptibility *and* a failure of self-tolerance housekeeping that drives SLE-like autoimmunity. This places C3 deficiency firmly on the **complement-SLE axis** alongside C1q, C4, and C2, with the modern mechanistic overlay that defective clearance converges on **type I interferon** activation — the rationale for emerging interferon-targeted therapy.

Complement defect	CH50	AH50	C3	C4	Dominant phenotype
Primary C3 deficiency	↓ ↓	↓ ↓	undetectable	normal	Infection + SLE/MPGN
C1q / C4 / C2 deficiency	↓ ↓	normal	normal/low	low (C4)	SLE > infection
Factor H / I deficiency	variable	↓	secondarily low	normal	aHUS/GN + infection
C3 nephritic factor	—	↓	low (acquired)	normal	C3 glomerulopathy
Terminal (C5–C9)	↓	↓	normal	normal	Neisseria infection

Evidence Base

PMID	Title (abbrev.)	Evidence type	Supports
42445183	Novel homozygous C3 splice-site variant (case report)	Human clinical	Rarity (<50 cases), AR inheritance, lab signature, phenotype, example variant (F001, F002, F008)
25037634	Are complement deficiencies really rare?	Review	Early-complement/autoimmune link; 1–10% of PIDs (F002, F008)
33563058	Lupus in children with PID	Human cohort	C3 deficiency among monogenic lupus (F002, F009)
42175904	Infection risk with complement inhibitors	Review	Core C3 effector functions (F003)
38032267	Complement receptor of Ig superfamily (CRIg)	Structural/in vitro	C3 cleavage products recognized by phagocyte receptor (F003)
16177781	Structures of C3	Structural	1,641-residue protein; thioester mechanism; central role (F005, F012)
12496386	Impaired Ab response in C3/Cr2-deficient mice	Model organism	Humoral defect to polysaccharide (F006)
28710441	IgG3-antigen complexes on FDCs need C1q/C3	Model organism	Immune-complex trafficking (F006)
39737181	C3 deficiency promotes pulmonary inflammation	Model organism	C3 ^{-/-} model; regulatory role (F006)
16138437	Factor I deficiency, IC glomerulonephritis	Human clinical	Secondary C3 consumption (F007)
6545495	Complement activation in renal disease	Review	FH/FI deficiency lowers C3 (F007)
19640589	TMA and MPGN pathogenic principles	Review	C3NeF mechanism (F007)
37356020	Reducing infection risk in complement deficiency	Guideline/review	Pathogen spectrum (F004)
32164349	21-yr follow-up of C2 deficiency family	Human clinical	Prophylaxis → normal life (F004)

PMID	Title (abbrev.)	Evidence type	Supports
28078901	Recurrent meningitis & complement deficiency	Human clinical	Conjugate vaccines + antibiotic prophylaxis (F004)
42597478	Anifrolumab in C1q-deficient pediatric SLE	Human clinical	Monogenic lupus, IFN therapy (F009)
16836843	Pediatric PID overview	Registry	Complement deficiency ~1.1% of pediatric PID (F008)

Source-type note: Direct primary evidence for complete C3 deficiency is dominated by case reports and small series (the disease being ultra-rare). Mechanistic claims are buttressed by structural biology ([PMID: 16177781](#)), mouse-knockout studies, and extrapolation from the better-characterized C1q/C2/factor H/factor I deficiencies. These extrapolations are flagged as *inferred* where they extend beyond direct C3-deficiency data.

Limitations and Knowledge Gaps

- 1. Ultra-rarity limits epidemiology.** With <50 reported cases, there are no robust prevalence/incidence, sex-ratio, penetrance, or survival statistics; most data are anecdotal.
- 2. Genotype–phenotype correlation is undefined.** Whether specific C3 variant classes predispose to the infection-predominant vs autoimmune-predominant phenotype is unknown ("the genetic and phenotypic spectrum remains incompletely defined," [PMID: 42445183](#)).
- 3. Mechanistic extrapolation.** The autoimmune/type-I-interferon mechanism and the therapeutic rationale (anifrolumab) are strongest for C1q deficiency and are extended to C3 deficiency by inference, not by dedicated C3-deficiency trials.
- 4. No disease-specific QoL or natural-history cohort data** exist.
- 5. Model-organism gaps.** C3^{-/-} mice reproduce opsonization/humoral defects but not the full human infection + SLE spectrum; some models even reveal a *protective* C3 role in tissue inflammation, indicating context dependence.

6. **Secondary vs primary hypocomplementemia** remains a frequent diagnostic pitfall; many "low C3" reports in the literature are secondary and must not be conflated with primary deficiency.

Proposed Follow-up Experiments / Actions

1. **Build an international C3-deficiency registry** aggregating all reported biallelic C3 cases with harmonized genotype, complement phenotype (C3/C4/CH50/AH50), infection history, and autoimmune/renal outcomes to enable the first genotype–phenotype and natural-history analyses.
2. **Curate and ACMG-classify the full C3 variant spectrum** (ClinVar/HGMD reconciliation), distinguishing LoF from hypomorphic alleles; correlate with residual C3 function.
3. **Prospectively evaluate vaccine responsiveness** (pneumococcal/meningococcal conjugate) in C3-deficient patients, informed by the mouse polysaccharide-response defect ([PMID: 12496386](#)), to optimize immunization schedules.
4. **Test interferon-targeted therapy (anifrolumab)** or other IFN-axis interventions in C3-deficiency-associated SLE, formally extending the C1q-deficiency rationale ([PMID: 42597478](#)).
5. **Explore C3-replacement / gene-directed approaches** (plasma-derived C3, hepatocyte-directed gene therapy — the liver being the main synthesis site) as potential disease-modifying strategies, currently absent.
6. **Standardize the diagnostic algorithm** (undetectable C3 + normal C4 + low CH50/AH50 → regulator panel [factor H/I, factor B] → C3NeF assay → C3 sequencing) to reliably separate primary from secondary hypocomplementemia.

Report compiled from 12 verified findings and 50 reviewed papers over 5 investigation iterations. Ontology suggestions (MONDO:0013417, HGNC:1318, UniProt P01024, HPO/GO/CL/UBERON/NCIT terms) are provided throughout for knowledge-base ingestion.
